REMARKS/ARGUMENTS

Claims 1-22 are pending and under examination. Claims 23-24 are canceled without prejudice to subsequent revival. No claim amendment should be construed as an acquiescence in any ground of rejection.

Rejections under 35 U.S.C. § 101 and § 112

Claims 23-24 are rejected under 35 U.S.C. § 112 as allegedly indefinite and under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. In response, applicants have canceled claims 23-24 while reserving the right to pursue them at a later time.

Rejection under 35 U.S.C. § 103(a)

Claims 1-22 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Shank *et al.* (WO 00/61138 A1) in view of Sachdeo (Topiramate: Clinical Profile in Epilepsy, Clin Pharmacokinet, May 1998, 34(5):335-346) and further in view of Brines *et al.* (WO 00-66164). Applicants submit that a proper *prima facie* case of obviousness under 35 U.S.C. § 103(a) cannot be set forth over the cited references for the reasons set forth below.

The Action characterizes Shank as teaching a method for treating chronic neurodegenerative disorders comprising administering a sulfamate carbohydrate or carbocyclic compound; Sachdeo as teaching the use of topiramate as adjunctive therapy for treating epilepsy; and Brines as teaching the use of erythropoietin for the treatment of various neurological disorders. According to the Action, it would have been obvious to one of ordinary skill in the art to combine fructopyranose sulfamate and erythropoietin into a single

composition for the treatment of neurological disorders. In response, applicants respectfully traverse.

A. A Proper Prima Facie Case of Obviousness Has Not Been Set Forth

To construct a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See*, MPEP § 2142. Moreover, to avoid the pitfall of hindsight, the Examiner must "identify ***specifically*** . . . the reasons one of ordinary skill in the art would have been motivated to select the references and combine them," *In re Rouffet* 47 USPQ2d 1453, 1459 (Fed. Cir. 1998). Applicants respectfully submit that each of the required criteria set forth above has not been satisfied, thus, a *prima facie* case of obviousness has not been set forth.

1. There is no Motivation to Combine the Cited References

The present invention is based, in part, on the surprising discovery that when a fructopyranose sulfamate and erythropoietin are co-administered for the treatment of neurological disorders, a synergistic effect is achieved. Accordingly, the present claims are directed to methods of treating neurological dysfunction comprising co-therapy with both a fructopyranose sulfamate **and** erythropoietin. In direct contrast, the cited references discuss the use of fructopyranose sulfamates **or** erythropoietin for the treatment of various neurological disorders. There is no specific suggestion that a fructopyranose sulfamate and erythropoietin should be combined *per se* and/or that the combination would give rise to a

reasonable expectation of success. It appears to be the Action's position, that if a combination of therapies is claimed, and references individually suggest the use of each agent alone, then it is obvious to combine the two agents for treatment. Applicants contend that such a position is untenable. For example, it is certainly not advisable to administer two antibiotics together to treat a particular infection. Such administration can be highly detrimental to the patient. Accordingly, applicants submit that there is simply no motivation provided in the cited references to administer both a fructopyranose sulfamate and erythropoietin in the treatment of neurological disorders.

2. The Cited References Fail to Provide a Reasonable Expectation of Success

To set forth a proper *prima facie* case of obviousness, it must be shown that one of skill would have derived from the combination of references a reasonable expectation of success in undertaking the claimed methods. Applicants respectfully submit that the combination does not provide the necessary reasonable expectation of success. In fact, Applicants submit that the Sachdeo reference actually teaches away from the methods of the present invention.

The Sachdeo reference discusses the pharmacokinetic properties and clinical profile of topiramate, an antiepileptic drug approved as adjunctive therapy with other antiepileptic drugs ("AEDs") for partial-onset seizures in adults. Despite the author's conclusion that topiramate, in some instances, is effective as an adjunctive therapy with other AEDs, a closer reading of the Sachdeo reference suggests that topiramate **is not** a good candidate for use in combination drug therapy. For instance, on page 337 of the Sachdeo reference, it is stated that topiramate plasma concentrations are reduced by as much as one half when topiramate is administered with other AEDs as compared to topiramate plasma concentrations when

topiramate is administered as a monotherapy. Based on these results, the author suggests that a significantly higher dose of topiramate is necessary when administered as adjunctive therapy. Because of the side-effects associated with topiramate therapy, including symptoms ranging from fatigue, fever, and malaise to hypokinesia, vertigo, stupor, convulsions grand mal, hyperkinesia, hypertonia, memory problems and eye disorders, the need for higher dosages of topiramate when administered as an adjunctive therapy discourages its use in combination therapy. Additionally, the authors found that patients on a regimen of topiramate and one or more other AEDs did not fare significantly better than patients on a regimen of topiramate alone. For example, a total of 46% of patients receiving 1000 mg/day of topiramate, in a monotherapy regime, achieved seizure reductions of greater than 50% whereas only 38% to 52% of patients receiving topiramate adjunctive therapy of 1000 mg/day achieved seizure reduction of greater than 50% (See page 341,Table III, and page 342). As the case law mandates, "[i]t is impermissible within the framework of Section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965). Accordingly, applicants submit that the Sachdeo reference cannot be said to provide a reasonable expectation of success that co-therapy with erythropoietin and topiramate would be beneficial. Furthermore, neither the Brines nor Shank references even discuss the use of erythropoietin or topiramate in combination therapy. Thus, the cited references, either alone or in combination would not have provided one of skill with the requisite reasonable expectation of success.

A. Applicants' Methods Produce Surprising Results

As set forth above, a proper *prima facie* case has not been advanced against the instant invention. Furthermore, Applicants' methods provide surprising results, which are entirely unexpected in light of the disclosure of the cited references.

It is well settled in the courts that greater than expected results are evidence of nonobviousness, *See* MPEP 716.02(a). Moreover, evidence of a greater than expected result may be shown by demonstrating synergism, "evidence of a greater than expected result may also be show by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.,* 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir). A showing that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of significant practical advantage is sufficient to overcome a *prima facie* case of obviousness. *Ex parte The NutraSweet Co.,* 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991).

Applicants have discovered that when erythropoietin and topiramate are administered together, the combination of the two agents is such that the total combined effect is greater than the sum of the individual effects, *i.e.,* a synergistic effect is observed. For example, on pages 27-31 of the specification, Applicants provide 3 examples measuring the ability of erythropoietin alone, topiramate alone, and erythropoietin and topiramate together to increase neurite outgrowth in hippocampal and cortical cells. As demonstrated in tables 1-3, the combined measured effects of co-therapy with erythropoietin and topiramate were greater than those predicted by adding the sum of the individual effects of treatment with either erythropoietin or topiramate alone. These results are completely unexpected given the

teachings of Sachdeo. As previously discussed, adjunctive therapy with topiramate and other AEDs did not result in synergistic effects. In fact, in at least one instance, topiramate monotherapy was equally effective as topiramate adjunctive therapy. Accordingly, one of skill in the would have been surprised that the claimed methods provide such a markedly improved result. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSIONS

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicant submits that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested.

If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 215-576-0300.

Respectfully submitted,

Date: May 19, 2003

Leslie E. Aberman
Limited Recognition Under 37 CFR
§ 10.9(b) Attached.

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439